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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,988	LEONARD ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,10-12,18,20 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 8, 10-12,18, 20,32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 5, 8, 10-12, 18, 20 and 32-35 are pending. Claims 5, 10, 18, and 20 have been amended, claims 6, 7, 8, 9, 13-17, 19 and 21-31 have been canceled and claims 32-35 have been added by Applicant's amendment filed on 02-28-2008.

Response to arguments

At page 7 of remarks, Applicants argue that "the Office has withdrawn claim 8 from consideration as allegedly drawn to subject matter of a non-elected group (Group II). However, Applicants believe that claim 8 could be a member of elected Group I, as well as non-elected Group II. In particular, Applicants note that claim 20, which is directed to similar subject matter as claim 8, was assigned to both Groups I and II. Therefore, Applicants ask that claim 8 be rejoined and examined with the elected claims of Group I". Examiner has considered the argument persuasive. As such, restriction to claim 8 is withdrawn.

3. Therefore, claims 5, 8, 10-12, 18, 20 and 32-35 are currently under examination to which the following grounds of rejection are applicable.

Objections/rejections maintained in response to Applicant arguments or amendments:

Specification

Applicants have amended the specification at page 19, line 20, to insert a sequence identifier for the amino acid sequence "WSXWS" (i.e., SEQ ID NO:17) and Applicants have submitted a paper and computer-readable copies of the substitute sequence listing. However, Applicant failed to comply with 37 CFR 1.821-1.825 because they have not submitted a statement that the information recorded in computer readable form is identical to the written sequence listing are required. Thus the following item is required:

a statement that the information recorded in computer readable form is identical to the written sequence listing.

To be fully responsible for restriction, Applicant is required to comply with the Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.

Claim Rejections - 35 USC § 112 - written description

Claims 5, 8, 10-12, 18 and 20 remain rejected and new claims 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant has not provided a response that properly applies to the rejection of claims 5, 8, 10-12, 18, 20 and new claims 32-35 under 35 U.S.C. 112, first paragraph, written description requirement, but has provided a single response that is equally relevant to rejections of claims under 35 U.S.C. 112, first paragraph, written description requirement, and scope of enablement.

These are different rejections that merit separate responses as they pertain to different grounds of rejection. Please, note that the examiner's response to argument related to Applicant's traversal of enablement rejection appear in the paragraph below under rejection-Claim Rejections - 35 USC § 112 –scope of enablement.

Response to Applicant Arguments as they apply to rejection of Claims 5, 8, 10-12, 18 and 20 and new claims 32-35 under 35 USC § 112 - written description.

At page 8 of remarks, Applicants argue that "the pending claims, as amended, recite an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (i.e., human IL-21 polypeptide) or an agonist thereof, wherein the agonist retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor" . Moreover, applicants contend that "assays to determine receptor binding are known in the art. Additionally, the claims require that the IL-21 agonist produce the same physiological effect produced by binding of the IL- 21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20)". Thus Applicants argue that based on the disclosure, one of skill in the art would had known the correlation between the function and the structure of an agonist of SEQ ID No. 1. Such is not persuasive.

While applicant arguments partially overcome some of the issues by identifying the IL-21 polypeptide to the amino acid sequence of SEQ ID No. 1, some additional issues remain that are discussed below. Amended claims 1 and 18, and new claims 34 and 35 are drawn to a genus of

agonists of SEQ ID No. 1 and a genus of amino acid sequences which differs by one, two, three, four or five amino acids from the amino acid sequence of SEQ ID No.1, respectively. The specification mentions only the full length IL-21 of SEQ ID No. 1. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the fragments of SEQ ID No. 1 binding the IL-21 receptor and having the claimed physiological activity based on the teachings in the specification. The specification does not disclose regions or domains of the protein that are essential to bind the IL-21 receptor resulting in the claimed physiological effects. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. There is not structure/function relationship taught at all for SEQ ID No. 1. Further, there is no teaching of how many amino acids may be deleted from either or both the N- and C-terminals and retain function. Therefore, the specification does not describe the claimed fragments of SEQ ID No. 1 binding to the IL-21 receptor and being functionally active in such full, clear, concise and exact terms so as to indicate that Applicant has possession of a genus of agonists of SEQ ID No. 1 and a genus of amino acid sequences which differs by one, two, three, four or five amino acids from the amino acid sequence of SEQ ID No.1 at the time of filing the present application.

Claim Rejections - 35 USC § 112 –scope of enablement

To the extent that the claims read on *ex vivo* methods for enhancing an immune response in a subject or treating a subject with a condition comprising a specific deficiency of at least one of memory B and plasma cells, the following rejection apply.

Claims 5, 8, 10-12, 18 and 20 remain rejected and new claims 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for claims directed to an *ex vivo* method of enhancing an immune response to a viral antigen or treating a subject with a condition comprising a specific deficiency of at least one of memory B and plasma cells comprising isolating a population of cells from the subject comprising one or more of a mature B cell and a cell progenitor, contacting said population with IL-21 of SEQ ID No. 1 or agonists of SEQ ID No. 1, so as to induce differentiation of said B cells into a memory B cell and a plasma cell, respectively, wherein the population is optionally contacted with an antigen, isolating said a memory B cell and a plasma cell and introducing said population into the subject.

Response to Applicant Arguments as they apply to rejection of Claims 5, 8, 10-12, 18 and 20 and new claims 32-35 under 35 USC § 112 - scope of enablement.

At page 8 of remarks, Applicants argue that "the pending claims, as amended, recite an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (i.e., human IL-21 polypeptide) or an agonist thereof, wherein the agonist retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor". Moreover, applicants contend that "assays to determine receptor binding are known in the art. Additionally,

the claims require that the IL-21 agonist produce the same physiological effect produced by binding of the IL- 21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20)". Thus Applicants argue that based on the disclosure, one of skill in the art would had known how the correlation between the function and the structure of the agonists of SEQ ID No. 1. Such is not persuasive.

While applicants' arguments partially overcome some of the issues by identifying the IL-21 polypeptide to the amino acid sequence of SEQ ID No. 1 and inserting the limitation in claims 5 and 18 related to the cell population being isolated and administered to the same subject, some additional issues remain that are discussed below. Amended claims 1, 18 and new claims 34 and 35 are drawn to a genus of agonists of SEQ ID No. 1 and a genus of amino acid sequence which differs by one, two, three, four or five amino acids from the amino acid sequence of SEQ ID No.1, respectively. The specification mentions only the full length IL-21 of SEQ ID No. 1 which binds the IL-21 receptor to induce differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the fragments of IL-21 of SEQ ID No. 1 binding the IL-21 receptor and having the claimed physiological activity based on the teachings in the specification. The specification does not teach regions or domains of the protein that are essential to bind the IL-21 receptor resulting in the claimed physiological effects. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core

of the protein. There is no teaching of how many amino acids may be deleted from either or both the N- and C-terminals and retain function. Neither prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of agonists of SEQ ID No. 1 and a genus of amino acid sequence which differs by one, two, three, four or five amino acids from the amino acid sequence of SEQ ID No.1 able to bind the IL-21 receptor to induce differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant invention to identify an enormous number of amino acids fragments of SEQ ID No. 1 retaining the claimed functionality.

At page 8 of Remarks, Applicants notes that "the Office also contends that the specification is not enabling for *ex vivo* methods of therapy. In particular, the Office contends that the specification does not provide any examples of *ex vivo* therapy or therapy against a viral antigen. The Office contends that memory B cells and plasma cells neutralize extracellular pathogens, but that a viral antigen is considered to be an intracellular antigen, such that antibody generation would require co- exposure of the B cell population to a viral antigen", however, Applicants argue that " there is no requirement for working examples in the specification for an enabling specification". Moreover, Applicants argue that "the specification discloses that a population of cells (e.g., B cell progenitors) that have been isolated from a subject can be contacted with IL-21 polypeptide or an IL-21 agonist, which results in the differentiation of the B cells into plasma cells and/or memory ceils, which are then isolated (see, e.g., page 34, line 18,

through page 35, line 3; and Examples 3-5). Furthermore, the specification discloses the administration of the isolated memory B cells and plasma cells to the subject to enhance an immune response (see, e.g., page 34, line 18, through page 35, line 3). Since antibody production (e.g., by plasma cells) is an essential element of the immune response, one of ordinary skill in the art would recognize that the inventive methods would be effective in enhancing an immune response in a subject". Further, applicants argue that claims 5 and 18 have been amended to recite that the method "optionally comprises the administration of an antigen to the B cell population". As such the disclosure provides sufficient guidance to enable the instant claims. Such is not persuasive.

The instant claims broadly a method for inducing an immune response against a viral infection comprising isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from said subject, contacting said cells with IL-21 so as to induce differentiation of said B cells into a memory B cell and a plasma cell, respectively, purifying or isolating said memory B cell and a plasma cell and introducing this population into the subject. Claim 5 recites that cells are contacted with a composition comprising an antigen in the alternative form. However, it is unclear how an immune response against a viral infection is effective merely **by a humoral response** e.g., a memory B cell and a plasma cell that are administered back to the subject after isolation, as viruses are intracellular pathogens and an effective response against intracellular viral pathogens involves processing and association of the viral antigen to be presented with the MHC Class I molecule on APC cell surface for activation of T cells to induce a cell-mediated immunity. In other words, the instant claims are drawn to methods for inducing an immune response against viral antigens, however, the presence of

antibodies in serum (e.g., a memory B cell and a plasma cell) may be directed against irrelevant or non-critical viral antigens, or the viral infection may be a type that is not controlled at all by antibodies such as the in the case of intracellular herpes viruses infections (see, Mims et al., Medical Microbiology, third edition, 2004, pp. 150-152). In contrast to applicant arguments, the presence of viral antigens in serum against envelope viral proteins such antibodies against the HIV-1 envelope gp120 and gp41does not imply an immune protective response, as the simply binding of the antibody molecule to the microbial surface do not necessary blocks HIV-1 entry into the target cell. In fact most treatment of HIV-infected individuals requires an intact cell-mediated immunity response for effective defense (Mims et al., Medical Microbiology, third edition, 2004, pp. 429-431). Additionally, amended claims 18 and 20 are broadly drawn to *ex vivo* treatment of an immunocompromised host e.g., a subject with a condition comprising a deficiency of a memory B cells and a plasma cells. As stated in the previous office action, the specification does not disclose any examples of an *ex vivo* method of treating a subject with a condition characterized by a deficiency of at least a memory B cells and a plasma cells. Though an enabling disclosure does not required working examples, the instant claims have been examined in accordance with the *Wands* factors and the teachings of the specification **as a whole**. The *Wands* factors include the presence or absence of working examples and to the extent the instant rejections are not sufficiently supported by an enabling disclosure in combination the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims, the disclosure is not enabling for the breadth of the claims. It is noted that post filing art discloses *ex vivo* therapy methods in relation to enhancement on tumor-specific $CD8^{+}$T cell responses by IL-21 and not *ex*

vivo treatment of an immunocompromised subject with administration of at least a memory B cells and a plasma cells. The specification as filed fails to provide particular guidance to resolve the known unpredictability in the art associated with treatment of an immunocompromised subject. The quantity of experimentation required to practice the methods as claimed would require the *de novo* determination of effective target sites, modes of delivery, safe administration of at least a memory B cells and a plasma cells to target appropriate cells and/or tissues in an immunocompromised subject, and further whereby treatment effects are provided for the claimed condition. Since the specification fails to provide particular guidance for the treatment of an immunocompromised subject comprising administration of at least a memory B cell and a plasma cell and the art teaches that treatment of a B cell deficient subject is highly unpredictable as evidence in the treatment of an immunocompromised HIV-infected individuals requiring an intact cell-mediated immune response, it would require undue experimentation to practice the invention as presently claimed. Hence, the scope of the patent protection sought by the Applicant as defined by the claim fails to correlate with the scope of enabling disclosure set forth in the specification.

New grounds of objection/rejection

Claim objection

The numbering of claims submitted in the amendment filed on 01-17-208 is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively

beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 32 and 33 should be renumbered to claims 34 and 35 after claims 32 and 33.

Conclusion

Claims 5, 8, 10-12, 18, 20 and 32-35 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Maria Leavitt/
Maria Leavitt
Examiner, Art Unit 1633.